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ORIGINAL RESEARCH

Enzalutamide in Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer: An Asian Multiregional, Randomized Study

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ABSTRACT

Introduction: Enzalutamide significantly improved clinical outcomes compared with placebo in patients with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) with disease progression despite androgen deprivation therapy (ADT) in the PREVAIL study. However, few patients from Asia were enrolled. Our study (NCT02294461) aimed to evaluate the safety and efficacy of enzalutamide in this disease setting in patients in mainland China, Korea, Taiwan, and Hong Kong.

Methods: In this double-blind, phase III study, patients with asymptomatic/mildly symptomatic metastatic prostate cancer and disease progression despite ADT were randomized to enzalutamide (160 mg/day) or placebo. The primary endpoint was time to prostate-specific antigen (PSA) progression. Secondary endpoints

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included overall survival, radiographic progression-free survival, time to first skeletal-related event (SRE), time to initiation of cytotoxic chemotherapy, PSA response ≥ 50%, best overall soft-tissue response, and safety. Pre-planned interim analysis was scheduled following approximately 175 PSA-progression events (67% of targeted total of 261 events). An additional 5-year landmark analysis of overall survival, time to antineoplastic therapy, and safety was performed.

Results: The double-blind study period was stopped after interim analysis owing to the benefit of enzalutamide over placebo. Overall, 388 patients were randomized (enzalutamide, $n = 198$; placebo, $n = 190$). Baseline characteristics were balanced between treatment groups. Enzalutamide significantly reduced risk of PSA progression vs placebo (hazard ratio 0.38; 95% CI 0.27–0.52; $P < 0.0001$). Median time to PSA progression was 8.31 months with enzalutamide and 2.86 months with placebo. Secondary endpoints, including 5-year overall survival, were significantly improved with enzalutamide, except time to first SRE. Adverse-event incidence was similar between enzalutamide and placebo. Fatigue was the most common drug-related adverse event in both treatment groups.

Conclusion: Enzalutamide significantly reduced risk of PSA progression, improved secondary efficacy endpoints, and was well tolerated in chemotherapy-naïve Asian patients with mCRPC with disease progression despite ADT.

Trial Registration: www.clinicaltrials.gov NCT02294461.

Keywords: Enzalutamide; Metastasis; Castration-resistant prostate cancer; Treatment efficacy; Asia

Key Summary Points

Why carry out this study?

In the PREVAIL study, enzalutamide significantly improved clinical outcomes compared with placebo in patients with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) with disease progression despite androgen deprivation therapy (ADT). However, few patients from Asia were enrolled.

Therefore, this study was conducted to evaluate the safety and efficacy of enzalutamide in a larger number of patients from Asia.

What was learned from the study?

Enzalutamide significantly reduced the risk of prostate-specific antigen progression vs placebo (hazard ratio 0.38; 95% CI 0.27–0.52; $P < 0.0001$), significantly improved most secondary endpoints, including overall survival and radiographic progression-free survival, and was well tolerated.

Efficacy and safety results from this study were generally consistent with those from the larger PREVAIL study.

Enzalutamide is an effective and well-tolerated treatment for chemotherapy-naïve Asian patients with mCRPC with disease progression despite ADT.

INTRODUCTION

Prostate cancer is the second most frequently diagnosed cancer in men worldwide, with lower incidence rates in Asia (6–29 per 100,000) than in Europe and North America (46–83 per 100,000) [1]. Incidence rates, however, have steadily increased in some Asian regions, including South Korea (15.1% per year) [2],

Hong Kong (7.1% per year) [3], and mainland China (4.7% per year) [4]. Indeed, the mortality-to-incidence ratio in Asia is 42.1%, compared with 23.1% and 13.1% in Europe and North America, respectively [5]. This can be attributed to the absence of a routine prostate-specific antigen (PSA) screening process in Asia, resulting in delayed diagnosis of patients; most patients are diagnosed with advanced or late-stage disease [6].

Androgen deprivation therapy (ADT) is a common treatment option for prostate cancer in Asia [7]. Despite effective suppression of serum testosterone, the majority of patients eventually experience disease progression to metastatic castration-resistant prostate cancer (mCRPC) [8, 9]. Progression is associated with increased serum PSA, suggesting the disease continues to be driven by androgen receptor signaling. Enzalutamide, an androgen receptor inhibitor, demonstrated significantly improved radiographic progression-free survival (rPFS) and overall survival (OS) vs placebo in both chemotherapy-naïve (PREVAIL; NCT01212991) and post-chemotherapy (AFFIRM; NCT00974311) patients with mCRPC [10, 11]. However, the PREVAIL trial only included a small proportion of patients from Asian countries (enzalutamide, 85/872 [9.7%]; placebo, 82/845 [9.7%]) [10], and as a result of differences in clinical practice in this region, a separate study with a larger number of patients from Asia was needed to further evaluate the efficacy and safety of enzalutamide in Asian men.

The study presented here thus aimed to assess the efficacy and safety of enzalutamide vs placebo in chemotherapy-naïve patients with mCRPC with disease progression despite treatment with ADT in mainland China, Korea, Taiwan, and Hong Kong.

METHODS

Study Design and Participants

This was a randomized, double-blind, placebo-controlled, phase III study of enzalutamide conducted in mainland China, Korea, Taiwan, and Hong Kong (NCT02294461). Eligible patients had histologically confirmed metastatic prostate cancer and disease progression (PSA, soft tissue, or bone) with ongoing ADT (gonadotropin-releasing hormone analogue or bilateral orchiectomy). Other inclusion criteria included asymptomatic or mildly symptomatic prostate cancer (Brief Pain Inventory–Short Form [BPI-SF], question 3, score < 4), a maximum serum testosterone level of 1.73 nmol/L, and Eastern Cooperative Oncology Group performance status of 0 or 1. Exclusion criteria included prior use of cytotoxic chemotherapy, radiation or radionuclide therapy for metastases, or abiraterone acetate. Additional exclusion criteria are provided in Appendix 1 in the supplementary material. Continued ADT was required. Disease progression definitions at study entry are provided in Table S1 in the supplementary material. Bisphosphonates and other approved bone-targeting agents for the treatment of metastatic prostate cancer were conditionally permitted.

The study was approved by the independent review board at each site (Table S2 in the supplementary material) and conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent before participation. Following screening, eligible patients were centrally randomized 1:1 according to a computer-generated, permuted-block randomization schedule, stratified by the investigative site, to receive enzalutamide (160 mg/day) or placebo. All patients, investigators, and study staff were blinded to treatment assignment. Treatment continued for as long as the patient tolerated the study drug and was continuing ADT, until centrally confirmed PSA and radiographic disease progression and initiation of cytotoxic chemotherapy or another investigational agent. Patients had a safety follow-up visit 28 days after their last dose of study drug or 1 day before initiation of cytotoxic chemotherapy or another investigational agent for treatment of prostate cancer, whichever occurred first. After study drug discontinuation, all patients had to undergo long-term follow-up to assess survival, subsequent treatments for prostate cancer, the first skeletal-related event (SRE), centrally confirmed PSA progression, and centrally

confirmed radiographic progression. After the occurrence of the first SRE, centrally confirmed PSA progression, and centrally confirmed radiographic progression, assessment could be completed by telephone.

On 12 December 2015, an independent data-monitoring committee recommended to halt the double-blind period of the study owing to compelling clinical benefit of enzalutamide over placebo. All ongoing enzalutamide-treated patients and ongoing and previously placebo-treated patients were offered the opportunity to receive open-label enzalutamide if they met the inclusion criteria and not the exclusion criteria. Patients who were not eligible to receive enzalutamide in the open-label period and patients who did not consent to open-label treatment but did not withdraw consent from the study continued long-term follow-up assessments per protocol. All patients were followed for survival or date of death during long-term follow-up. Long-term follow-up data were collected every 12 weeks up to a 5-year landmark analysis.

Study Endpoints

The primary endpoint was time to PSA progression (TTPP), defined as the time from randomization to PSA progression, according to the consensus guidelines of the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) [12]. For patients with a PSA decline at week 13, the PSA progression date was defined as the date when an increase of least 25% and an absolute increase of at least 2 ng/mL above the nadir was documented, which was confirmed by a second consecutive value obtained 3 or more weeks later. Secondary endpoints included OS, rPFS, time from randomization to first SRE, time from randomization to initiation of cytotoxic chemotherapy, PSA response $\geq$ 50%, and best overall soft-tissue response. Exploratory endpoints included the Functional Assessment of Cancer Therapy–Prostate (FACT-P), European Quality of Life 5-Domain Scale (EQ-5D), and BPI-SF questionnaires, measuring quality of life (QoL). An updated analysis of OS was performed, in addition to an exploratory analysis of time to subsequent antineoplastic therapy, using data as of the 5-year data cutoff. More details about endpoint definitions are provided in Table S1 in the supplementary material.

Assessments

PSA was assessed at screening, weeks 1 and 13, and every subsequent 4 weeks. Radiographic disease progression was evaluated according to PCWG2 and Response Evaluation Criteria in Solid Tumors, version 1.1, by CT/MRI and bone scan at screening, weeks 9, 17, 25, and 37, and every subsequent 12 weeks. FACT-P and EQ-5D were assessed at weeks 1, 5 (FACT-P only), 13, 25, 37, and every subsequent 12 weeks. Time to degradation of FACT-P was calculated as time from randomization to date of post-baseline degradation. EQ-5D scale and mean health state scores were assessed at each visit. Rate of pain progression was assessed using the BPI-SF, measured at baseline, 3 months, and 6 months. Safety was assessed at every study visit until the safety follow-up.

Statistical Analyses

A sample size of 400 patients (200 in each treatment group), corresponding to 261 PSA progression events, was planned, on the basis of a target hazard ratio (HR) of 0.67, a two-sided type I error of 0.05, and a power of 90%. Interim analysis was planned when approximately 175 PSA progression events (67% of 261) occurred. The interim analysis presented here was performed when 158 events (61% of 261) had occurred. Experts in prostate cancer, clinical trial safety monitoring, and statistics comprised the independent data-monitoring committee responsible for evaluating the efficacy and safety data at the interim analysis. Efficacy and QoL analyses were conducted on the intent-to-treat population, defined as all randomized patients analyzed. Safety analyses were conducted on the safety analysis set, defined as all randomized patients who received at least one dose of the study drug.

Data were summarized descriptively using SAS® version 9.3 (Cary, NC, USA) or higher. The unstratified Cox proportional hazards model

Table 1 Patient demographics and baseline disease characteristics (intent-to-treat population)

	Enzalutamide (*n* = 198)	**Placebo (*n* = 190)**
Age, years, median (range)	71 (51–89)	71 (50–88)
Age category, years, *n* (%)		
< 65	47 (23.7)	47 (24.7)
65–74	81 (40.9)	73 (38.4)
75–84	60 (30.3)	58 (30.5)
≥ 85	10 (5.1)	12 (6.3)
BMI, kg/m^2, mean (± SD)	24.5 (± 3.1)	24.8 (± 3.2)
Baseline ECOG performance status, *n* (%)		
0	113 (57.1)	124 (65.3)
1	85 (42.9)	66 (34.7)
BPI-SF, question 3 (worst pain in last 24 h), *n* (%)		
0–1	136 (68.7)	125 (65.8)
2–3	62 (31.3)	65 (34.2)
Prior use of corticosteroids for prostate cancer, *n* (%)	11 (5.6)	10 (5.3)
Baseline use of daily oral corticosteroids > 7 days in duration, *n* (%)	0	0
History of cardiovascular disease, *n* (%)	15 (7.6)	17 (8.9)
Time since diagnosis, months, median (range)	30.25 (0.4–161.9)	30.80 (0.7–214.8)
Baseline PSA, μg/L, median (range)	56.2 (2.5–5000.0)	62.5 (1.5–2412.0)
Total Gleason score, *n* (%)		
2–4	0	0
5–7	56 (28.3)	63 (33.2)
8–10	138 (69.7)	117 (61.6)
Missing	4 (2.0)	10 (5.3)
Distant metastasis at initial diagnosis, *n* (%)		
Mx/unknown	18 (9.1)	11 (5.8)
M0	39 (19.7)	46 (24.2)
M1	141 (71.2)	133 (70.0)
Distribution of disease at screening[a], *n* (%)		
Bone	186 (93.9)	176 (92.6)
Lymph node	54 (27.3)	46 (24.2)

Table 1 continued

	Enzalutamide (n = 198)	Placebo (n = 190)
Visceral (liver or lung)	24 (12.1)	16 (8.4)
Other soft tissue	48 (24.2)	52 (27.4)
Number of bone metastases at screening, n (%)		
0	0	0
1	20 (10.1)	16 (8.4)
2–4	41 (20.7)	43 (22.6)
5–9	50 (25.3)	41 (21.6)
10–20	43 (21.7)	45 (23.7)
> 20	32 (16.2)	31 (16.3)
Missing	12 (6.1)	14 (7.4)

BMI body mass index, *ECOG* Eastern Cooperative Oncology Group, *PSA* prostate-specific antigen, *BPI-SF* Brief Pain Inventory–Short Form, *M0* non-metastatic, *M1* metastatic, *Mx* cannot be measured
[a]Patients can be included in > 1 category

(covariate = treatment group) and log-rank test (two-sided significance level = 0.05) were used to assess TTPP, OS, rPFS, time to first SRE, and time to initiation of cytotoxic chemotherapy. TTPP, OS, and rPFS were also assessed using the Kaplan–Meier method. The unstratified Cochran–Mantel–Haenszel score test and Clopper–Pearson method were used to assess PSA response ≥ 50% and best overall soft-tissue response. Time to degradation of FACT-P was estimated using the Kaplan–Meier product limit methods; HRs and 95% CIs were estimated using an unstratified Cox regression model. The statistical significance of the difference in pain progression rate was assessed using Fisher's exact test.

RESULTS

Primary Analysis

Patient Disposition, Demographics, and Baseline Characteristics

From 23 April 2014 through 20 September 2015, 388 patients were randomized from 46 sites in mainland China, Korea, Taiwan, and Hong Kong (enzalutamide, 198; placebo, 190). Patient baseline demographic and disease characteristics were balanced between treatment groups (Table 1). Over 60% of patients in both treatment groups had a Gleason score ≥ 8, over 70% had metastatic disease at initial diagnosis, and approximately 10% had visceral disease. Nearly all (99%) patients had received at least one prior hormonal therapy (enzalutamide, 99.0%; placebo, 98.9%), with 23.7% having received at least four (enzalutamide, 21.7%; placebo, 25.8%). Baseline demographics and disease characteristics were generally balanced between treatment groups within each country (Table S3 in the supplementary material). Treatments that were administered secondary to disease progression are summarized in Table S4 in the supplementary material.

The data cutoff date for the primary analysis was 20 September 2015. All 388 patients received at least one dose of study drug (Fig. S1 in the supplementary material). Overall, 193 patients discontinued study treatment (enzalutamide, 62; placebo, 131), 114 of whom also discontinued long-term follow-up (enzalutamide, 34; placebo, 80). The most frequently reported primary reason for treatment

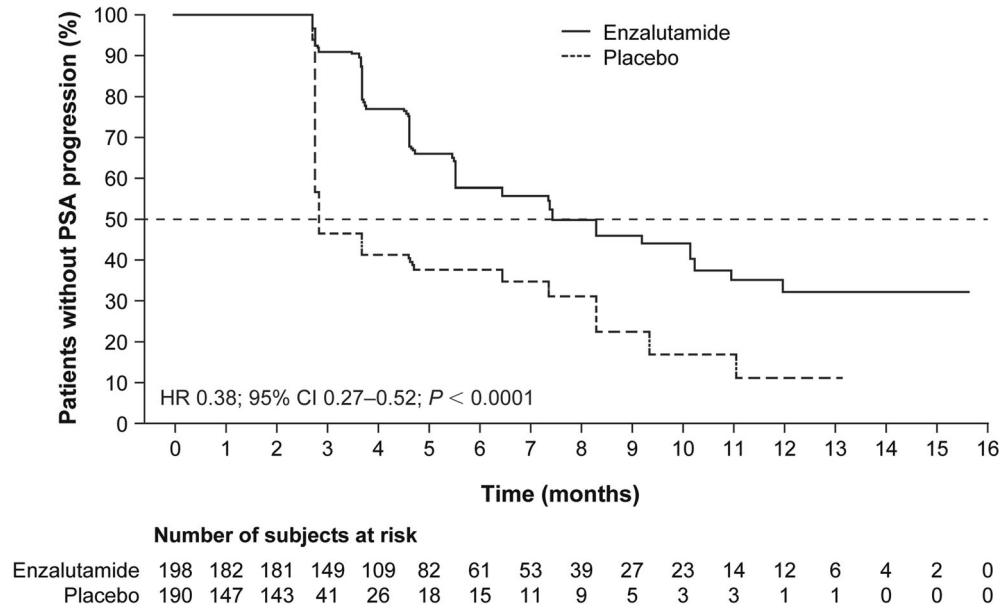

Fig. 1 Kaplan–Meier curves for time to PSA progression at primary analysis (intent-to-treat population). *CI* confidence interval, *HR* hazard ratio, *PSA* prostate-specific antigen

discontinuation during active treatment was disease progression, while withdrawn consent was the most common reason for discontinuation from long-term follow-up.

Primary Endpoint: Time to PSA Progression

Enzalutamide significantly reduced the risk of PSA progression compared with placebo (HR 0.38; 95% CI 0.27–0.52; $P < 0.0001$). Median TTPP was 8.31 months (95% CI 5.72–10.25) with enzalutamide vs 2.86 months (95% CI 2.83–4.63) with placebo. With enzalutamide, 78/198 (39.4%) patients had confirmed PSA progression vs 80/190 (42.1%) patients with placebo (Fig. 1).

Secondary Endpoints

OS As of the data cutoff date for the primary analysis, 33 deaths were reported: 11/198 (5.6%) in the enzalutamide group and 22/190 (11.6%) in the placebo group. Enzalutamide significantly reduced the risk of death compared with placebo (HR 0.33; 95% CI 0.16–0.67; $P = 0.0015$) (Fig. S2 in the supplementary material). A large majority of patients in both treatment groups ($n = 187$, 94.4% for enzalutamide; $n = 168$, 88.4% for placebo) were censored at the date last known alive or the data cutoff date, whichever occurred first. Median OS was not yet reached (NYR) with either treatment as of the cutoff date.

rPFS rPFS events were experienced by 40/198 (20.2%) patients with enzalutamide and 66/190 (34.7%) patients with placebo. Overall, enzalutamide significantly reduced the risk of radiographic progression or death compared with placebo (HR 0.31; 95% CI 0.20–0.46; $P < 0.0001$) (Fig. 2). Median duration of rPFS was NYR with enzalutamide vs 5.29 months (95% CI 3.61–11.33) with placebo.

Time to First SRE Seven of 198 (3.5%) patients in the enzalutamide group and nine of 190 (4.7%) patients in the placebo group experienced an SRE as of the data cutoff date. Enzalutamide was associated with a statistically nonsignificant 44% reduction in risk of a first SRE vs placebo (HR 0.56; 95% CI 0.21–1.52; $P = 0.2501$). Median time to first on-study SRE was NYR with either treatment.

Time to Initiation of Cytotoxic Chemotherapy Eight of 198 (4.0%) patients in the

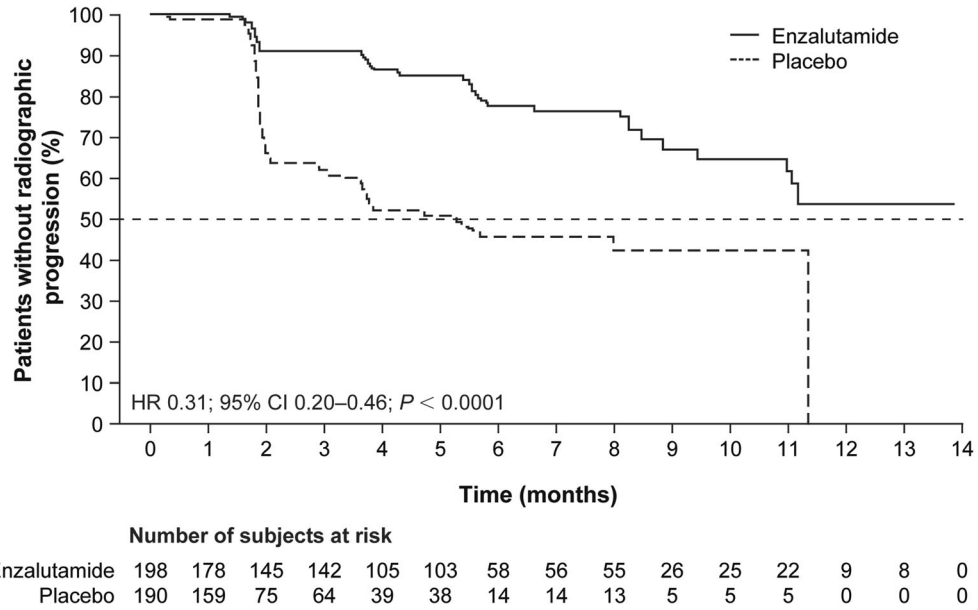

Fig. 2 Kaplan–Meier curves for time to radiographic progression at primary analysis (intent-to-treat population). *CI* confidence interval, *HR* hazard ratio

enzalutamide group and 18/190 (9.5%) in the placebo group initiated cytotoxic chemotherapy. Enzalutamide was associated with a significant delay in time to initiation of cytotoxic chemotherapy vs placebo (HR 0.28; 95% CI 0.12–0.66; $P = 0.0020$). Median time to initiation of cytotoxic chemotherapy was NYR with enzalutamide vs 13.93 months (95% CI NYR–-NYR) with placebo. In addition, use of subsequent antineoplastic therapies (cytotoxic or hormonal) was less common with enzalutamide (28/198; 14.1%) vs placebo (46/190; 24.2%).

PSA Response ≥ 50% Overall, 182/198 (91.9%) patients in the enzalutamide group and 148/190 (77.9%) in the placebo group had a baseline and at least one post-baseline PSA assessment and were included in the PSA response analysis. Of these patients, 120/182 (65.9%) in the enzalutamide group and 15/148 (10.1%) in the placebo group had a confirmed ≥ 50% reduction in PSA (difference in response rate 55.8%; 95% CI 47.4–64.2; $P < 0.0001$).

Best Overall Soft-Tissue Response Among patients with measurable soft-tissue disease at screening (enzalutamide, 65/198 [32.8%]; placebo, 60/190 [31.6%]), a significantly greater proportion of patients in the enzalutamide group had a best overall objective response (complete or partial response) vs the placebo group (18/65 [27.7%] vs 1/60 [1.7%]; $P < 0.0001$). Responses among the 65 patients in the enzalutamide group and 60 in the placebo group, respectively, were as follows: complete response, 4 (6.2%) and 0; partial response, 14 (21.5%) and 1 (1.7%); stable disease, 35 (53.8%) and 32 (53.3%); progressive disease, 7 (10.8%) and 17 (28.3%); not evaluable, 5 (7.7%) and 10 (16.7%).

Exploratory Endpoints

FACT-P In the enzalutamide group, nine patients (4.5%) had degradation of FACT-P vs seven patients (3.7%) in the placebo group (Table S5 in the supplementary material). Treatment with enzalutamide was associated with a 27% reduction in risk of FACT-P degradation (HR 0.73; 95% CI 0.27–1.99; $P = 0.54$). Median time to degradation of FACT-P was NYR in either group.

Table 2 Overview of AEs at primary analysis (safety population)

n (%)	Enzalutamide (*n* = 198)	Placebo (*n* = 190)
AEs	167 (84.3)	153 (80.5)
AEs leading to study drug discontinuation	26 (13.1)	34 (17.9)
AEs of special interest[a]	85 (42.9)	54 (28.4)
Drug-related AEs[b]	85 (42.9)	54 (28.4)
Drug-related AEs leading to study drug discontinuation	6 (3.0)	7 (3.7)
Grade 3 or higher AEs	49 (24.7)	56 (29.5)
SAEs	34 (17.2)	47 (24.7)
Drug-related SAEs	7 (3.5)	6 (3.2)
SAEs leading to study drug discontinuation	10 (5.1)	17 (8.9)
SAEs leading to death	7 (3.5)	6 (3.2)
Drug-related SAEs leading to death	0	0

AEs were recorded in the electronic case report form and graded on the basis of the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0, by the study investigators

AE adverse event, *SAE* serious adverse event

[a]AEs of special interest include convulsions, neutropenia, mental impairment, hallucinations, fractures, hypertension, hepatic impairment, renal impairment, major adverse cardiovascular events, select gastrointestinal events, venous thromboembolic events, and fatigue, all of which are previously identified risks associated with enzalutamide or AEs of clinical interest

[b]Drug-related AEs were defined as AEs with a possible or probable relationship to the study drug, as determined by investigators

EQ-5D At each visit through week 49, patients in the enzalutamide group had numerically higher health state scores vs patients in the placebo group (Table S5 in the supplementary material).

BPI-SF At month 6, progression of pain occurred in 22.5% of patients in the enzalutamide group vs 30.9% of the placebo group ($P = 0.26$) (Table S5 in the supplementary material); however, BPI-SF data at month 6 were collected in far more patients in the enzalutamide than placebo group (60.6% vs 28.9%).

Safety

Drug Exposure and Adverse Events Median treatment duration was 6.60 months (range 0.5–16.3) for enzalutamide and 3.70 months (range 0.2–12.8) for placebo. The majority (at least 90%) of patients did not undergo dose modifications during the study. At least one dose modification was recorded in 15/198 (7.6%) patients in the enzalutamide group and 14/190 (7.4%) patients in the placebo group, all of which were due to an adverse event (AE), except for 2/190 (1.1%) patients in the placebo group, which were due to other reasons. Fewer patients in the enzalutamide group vs the placebo group experienced AEs leading to study drug discontinuation (13.1% vs 17.9%) (Table 2). The overall incidence of patients reporting AEs was similar between treatment groups: 84.3% in the enzalutamide group vs 80.5% in the placebo group (Table 2). A higher incidence of patients in the enzalutamide group vs the placebo group reported AEs of special interest (AESIs) [42.9% vs 28.4%, respectively]. AESIs of fracture were reported in two (1.0%) patients in the enzalutamide group and in one (0.5%) patient in the placebo group; AESIs of mental impairment were reported in two (1.0%) patients in the enzalutamide group (memory impairment and cognitive disorder) and in no patients in the placebo group. A greater proportion of patients receiving enzalutamide vs placebo reported AEs considered by the investigator to be drug-related (42.9% vs 28.4%); however, the incidence of drug-related AEs leading to study drug discontinuation was similar between treatment groups (3.0% vs 3.7%).

Overall, 24.7% of patients in the enzalutamide group and 29.5% of patients in the placebo group reported AEs of grade ≥ 3 (Table 2). The incidence of serious AEs (SAEs) was lower in the enzalutamide group than in the placebo group (17.2% vs 24.7%, respectively), as was the

incidence of SAEs leading to study drug discontinuation (5.1% vs 8.9%). The incidence of drug-related SAEs was similar between treatment groups (3.5% vs 3.2%).

The most frequently reported AEs of any grade and grade ≥ 3 are presented in Table 3. The most frequently reported AEs of any grade considered by the investigator to be drug-related in the enzalutamide group were fatigue (17/198 [8.6%]), decreased appetite (14/198 [7.1%]), hypertension (11/198 [5.6%]), nausea (8/198 [4.0%]), and dizziness (8/198 [4.0%]). In the placebo group, fatigue (8/190 [4.2%]), decreased appetite (6/190 [3.2%]), nausea (6/190 [3.2%]), and anemia (6/190 [3.2%]) were the most frequently reported AEs of any grade assessed by the investigator to be drug-related. Grade ≥ 3 fatigue was experienced by a small number of patients (enzalutamide, 1/198 [0.5%]; placebo, 1/190 [0.5%]). No seizures or convulsions were reported with either treatment.

Eleven of 198 (5.6%) patients in the enzalutamide group and 22/190 (11.6%) patients in the placebo group died as of the data cutoff date. Disease progression was the most frequently reported cause of death (enzalutamide, 5/198 [2.5%]; placebo, 12/190 [6.3%]), followed by deaths due to other causes (enzalutamide, 5/198 [2.5%]; placebo, 5/190 [2.6%]) or unknown causes (enzalutamide, 1/198 [0.5%]; placebo, 4/190 [2.1%]). Of the 13 SAEs leading to death (Table S6 in the supplementary material), none were considered possibly drug-related by the investigator.

Table 3 Most common any grade and grade ≥ 3 AEs at primary analysis by system organ class and preferred term (safety population)

n (%)[a]	Enzalutamide (*n* = 198)	Placebo (*n* = 190)
AEs of any grade occurring in ≥ 5% of patients in either treatment group		
Musculoskeletal and connective tissue disorders	65 (32.8)	75 (39.5)
Back pain	19 (9.6)	18 (9.5)
Bone pain	12 (6.1)	25 (13.2)
Pain in extremity	14 (7.1)	17 (8.9)
Arthralgia	15 (7.6)	13 (6.8)
Musculoskeletal pain	10 (5.1)	5 (2.6)
Gastrointestinal disorders	59 (29.8)	53 (27.9)
Constipation	17 (8.6)	13 (6.8)
Nausea	14 (7.1)	9 (4.7)
General disorders/ administration site conditions	56 (28.3)	42 (22.1)
Fatigue	25 (12.6)	12 (6.3)
Pyrexia	10 (5.1)	13 (6.8)
Asthenia	10 (5.1)	7 (3.7)
Infections and infestations	44 (22.2)	27 (14.2)
Nasopharyngitis	13 (6.6)	6 (3.2)
Investigations	37 (18.7)	26 (13.7)
Decreased weight	10 (5.1)	10 (5.3)
Metabolism and nutrition disorders	34 (17.2)	23 (12.1)
Decreased appetite	24 (12.1)	17 (8.9)
Nervous system disorders	36 (18.2)	20 (10.5)
Dizziness	17 (8.6)	7 (3.7)
Renal and urinary disorders	24 (12.1)	24 (12.6)
Hematuria	7 (3.5)	13 (6.8)

Five-Year Analysis

Patient Disposition

The data cutoff date for the 5-year analysis was 4 November 2020. Seven additional patients (four enzalutamide, three placebo), all of whom received at least one dose of study drug and who were randomized after the primary data analysis cutoff date, were included in the 5-year analysis only.

Eighty-five patients (42.1%) in the enzalutamide group and 51 patients (26.4%) in the placebo group received treatment with

Table 3 continued

n (%)[a]	Enzalutamide (*n* = 198)	Placebo (*n* = 190)
Blood and lymphatic system disorders	17 (8.6)	17 (8.9)
Anemia	12 (6.1)	17 (8.9)
Vascular disorders	24 (12.1)	8 (4.2)
Hypertension	16 (8.1)	2 (1.1)
Psychiatric disorders	11 (5.6)	7 (3.7)
Insomnia	10 (5.1)	5 (2.6)
AEs of grade ≥ 3 occurring in ≥ 2% of patients in either treatment group		
Musculoskeletal and connective tissue disorders	7 (3.5)	14 (7.4)
Bone pain	3 (1.5)	7 (3.7)
Investigations	9 (4.5)	8 (4.2)
Infections and infestations	9 (4.5)	7 (3.7)
Lung infection	4 (2.0)	1 (0.5)
Renal and urinary disorders	4 (2.0)	9 (4.7)
Hematuria	2 (1.0)	4 (2.1)
Gastrointestinal disorders	8 (4.0)	4 (2.1)
Blood and lymphatic system disorders	4 (2.0)	7 (3.7)
Anemia	3 (1.5)	6 (3.2)
General disorders/ administration site conditions	3 (1.5)	7 (3.7)
Neoplasms benign, malignant, and unspecified	1 (0.5)	8 (4.2)
Vascular disorders	7 (3.5)	2 (1.1)
Hypertension	7 (3.5)	0
Metabolism and nutrition disorders	6 (3.0)	2 (1.1)
Cardiac disorders	5 (2.5)	3 (1.6)
Nervous system disorders	6 (3.0)	1 (0.5)
Respiratory, thoracic, and mediastinal disorders	1 (0.5)	6 (3.2)
Surgical and medical procedures	0	5 (2.6)
Chemotherapy	0	4 (2.1)

AE adverse event

[a]Percentage of patients reporting at least one AE within the specified system organ class

enzalutamide or placebo in the open-label period, while 16 patients (7.9%) in the enzalutamide group and nine patients (4.7%) in the placebo group were in long-term follow-up.

As of the 5-year analysis data cutoff date, 19 patients (9.4%) in the enzalutamide group and nine patients (17.6%) in the placebo crossover group were actively receiving study treatment. The most common reasons for treatment discontinuation across all treatment groups were disease progression and withdrawal of consent, while the main reasons for discontinuation from the study were death and withdrawal of consent to be followed.

OS

A total of 163 deaths were reported: 85/202 (42.1%) in the enzalutamide group and 78/193 (40.4%) in the placebo group. Enzalutamide significantly reduced the risk of death compared with placebo (HR 0.70; 95% CI 0.51–0.95; $P = 0.0208$) (Fig. 3). Median OS was 39.06 months (range 1.7–77.7) in the enzalutamide group and 27.10 months (range 0.3–76.0) in the placebo group.

Time to Subsequent Antineoplastic Therapy

Subsequent antineoplastic therapy for prostate cancer was reported in 36/202 patients (17.8%)

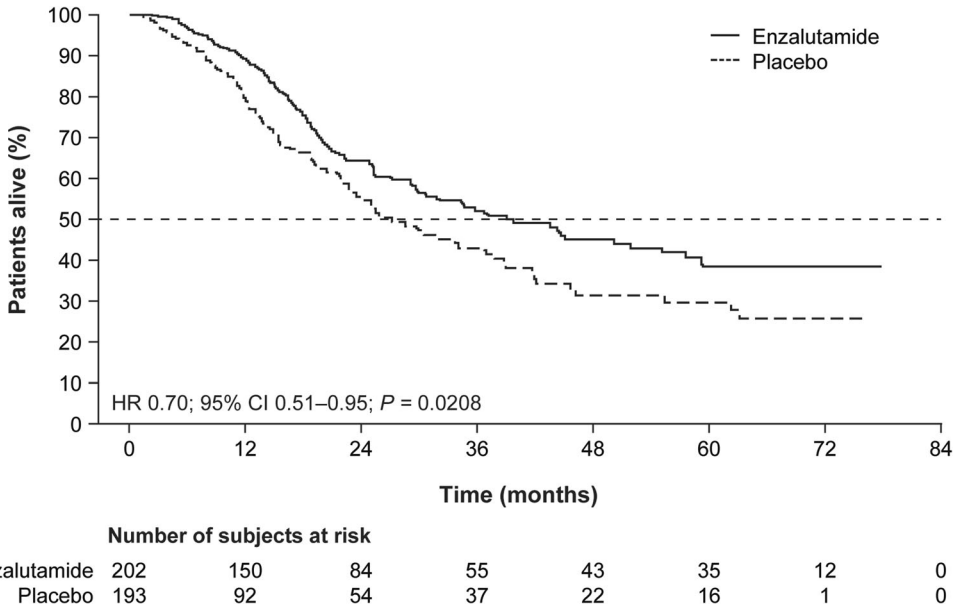

Fig. 3 Kaplan–Meier curves for percentage of patients alive at the 5-year analysis (intent-to-treat population). *CI* confidence interval, *HR* hazard ratio

in the enzalutamide group and 55/193 patients (28.5%) in the placebo group. The most common subsequent antineoplastic therapies for prostate cancer were docetaxel (enzalutamide, 24/202 [11.9%]; placebo, 27/193 [14.0%]) and abiraterone (enzalutamide, 21/202 [10.4%]; placebo, 36/193 [18.7%]). Median time to subsequent therapy was NYR in either treatment arm.

Safety

Median treatment duration was 13.25 months (range 0.5–77.3) for enzalutamide-treated patients, 4.00 months (range 0.2–18.6) for placebo-treated patients, and 22.00 months (range 0.2–53.8) for placebo crossover patients. The overall incidence of AEs, grade $\geq$ 3 AEs, AEs resulting in death, and SAEs was higher in the enzalutamide group compared with the placebo group (Table S7 in the supplementary material); differences in treatment duration between the two groups is likely to account for this disparity. The incidences of AEs were generally similar between the enzalutamide and placebo crossover groups across most categories (Table S7 in the supplementary material). The incidence of AEs leading to study drug discontinuation was similar across all three treatment groups (Table S7 in the supplementary material).

The most frequently reported AEs of any grade and grade $\geq$ 3 are reported in Table S8 in the supplementary material; no seizures or convulsions were reported in any treatment group. No new safety signals were identified.

AEs resulting in death were reported for 24/202 patients (11.9%) in the enzalutamide group, 7/193 patients (3.6%) in the placebo group, and 7/51 patients (13.7%) in the placebo crossover group. Three patients had AEs resulting in death that were considered study drug-related: two in the enzalutamide group (cardiac arrest and death) and one in the placebo crossover group (death).

DISCUSSION

In this study of Asian patients with minimally symptomatic or asymptomatic chemotherapy-naïve mCRPC that had progressed despite ADT, enzalutamide significantly improved TTPP and rPFS and was generally well tolerated. A longer duration of treatment with enzalutamide vs placebo was observed owing to the delay in PSA

progression and lower incidence of AEs leading to study drug discontinuation. Additionally, the incidence of drug-related SAEs was low and similar between treatment groups (less than 4% for either enzalutamide or placebo), with no drug-related SAEs leading to death in either group. Owing to the clinical benefit observed with enzalutamide, the independent data-monitoring committee recommended that the double-blind period of the study be stopped and that patients be offered open-label enzalutamide. Five years after the primary analysis for all other endpoints, a statistically significant reduction of 30% in the risk of death was observed in patients randomized to enzalutamide compared with placebo, despite approximately one-quarter of patients in the placebo group receiving open-label enzalutamide and more than one-quarter receiving a subsequent antineoplastic therapy. The safety profile of enzalutamide at the 5-year analysis was consistent with the primary analysis and no new safety signals were identified.

TTPP was selected as the primary endpoint in this study on the basis of strong associations with OS, the gold-standard endpoint, in a trial-level data analysis of 28 randomized controlled trials of medical treatments in mCRPC [13]. In the current study, treatment was continued until both PSA progression and radiographic disease progression were centrally confirmed to minimize premature discontinuation of treatment due to rising PSA levels alone.

Direct comparisons between this study and the PREVAIL trial of primarily European and North American patients with mCRPC are challenging because of differences in sample size and patient demographics, despite similar study entry criteria and endpoints. However, similar to PREVAIL, reported baseline patient demographics and disease characteristics were generally well balanced between treatment groups [10] (Table S9 in the supplementary material). Efficacy results were also largely consistent between the studies. Median TTPP with enzalutamide was longer in PREVAIL than in the current study (11.2 months vs 8.3 months, respectively) [10], attributable to the less-frequent PSA assessments in PREVAIL (generally every 3 months) vs the current study (every month after week 13). Both studies reported significant reductions in the risk of radiographic progression or death (PREVAIL, HR 0.19, 95% CI 0.15–0.23, $P < 0.001$; current study, HR 0.31, 95% CI 0.20–0.46, $P < 0.0001$). At the 5-year data cutoff, a greater reduction in risk of death was observed in this study (30%) than in PREVAIL (17%), possibly as a result of the lower number of subsequent antineoplastic treatments in the current study (enzalutamide, 18%; placebo, 29%) compared with PREVAIL (enzalutamide, 70%; placebo, 86%) [14]. The safety profile of enzalutamide was also generally consistent with that reported in PREVAIL at both analyses [10, 14], with no seizures or additional safety concerns. The findings of the current study are also consistent with those from a post hoc analysis in East Asian patients from the PREVAIL study [15]. In that analysis, enzalutamide reduced the risk of radiographic progression or death with an HR of 0.38 (95% CI 0.10–1.44), similar to the HR of 0.31 observed in this study. The benefit of enzalutamide in this study of Asian patients with mCRPC is therefore consistent with that of PREVAIL, supporting the use of enzalutamide as an effective and well-tolerated treatment option in this population.

Real-world data are available for the efficacy of enzalutamide in 199 chemotherapy-naïve Korean patients with mCRPC, although only 89 of the 199 patients received concurrent ADT as in the PREVAIL Asia study [16]. In the real-world study, 74.3% of patients achieved a PSA decline of $\geq$ 50% from baseline, vs 65.9% in the current study. The real-world efficacy of enzalutamide was also assessed in a retrospective study in Hong Kong in which 43.6% of chemotherapy-naïve, enzalutamide-treated patients achieved a PSA response ($\geq$ 50% decline); significantly longer PFS and OS were observed with earlier lines of enzalutamide therapy [17].

One limitation of this study was the high proportion of patients discontinuing treatment and long-term follow-up because of withdrawal of consent, particularly in the placebo group, which may have impacted the availability of longitudinal data in these patients. The first post-randomization PSA assessments were scheduled for week 13 (i.e., 12 weeks after

randomization). However, the median TTPP for placebo was reported as 2.86 months (95% CI 2.83–4.63), which is equivalent to 12.4 weeks. This difference can be attributed to the scheduling of clinic visits at some study sites.

These results provide a better understanding of the efficacy and safety of enzalutamide in Asian patients with chemotherapy-naïve mCRPC who had disease progression or ADT, and contribute to more effective disease management in clinical practice in this geographic region.

CONCLUSIONS

Overall, enzalutamide significantly delayed PSA progression, radiographic disease progression, the need for cytotoxic chemotherapy, and death in Asian men with minimally symptomatic or asymptomatic chemotherapy-naïve mCRPC. Five years after the primary analysis, enzalutamide significantly improved OS and continued to be well tolerated in this population. These results demonstrate that the efficacy and safety of enzalutamide previously shown in the PREVAIL study is also observed in this patient population, supporting the use of enzalutamide as a therapeutic option for Asian men with mCRPC.

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Compliance with Ethics Guidelines. The study was approved by the independent review board at each site, named in Table S2 in the supplementary material, and conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki.

Data Availability. Researchers may request access to anonymized participant-level data, trial-level data, and protocols from Astellas-sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

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